

**REMARKS**

Claims 1, 6-9, 12, 13, and 15-17 are presently pending on the record. Claims 1, 6-8, 12, and 13 have been amended. Claims 9 and 15-17 are canceled. New Claims 51-56 have been added.

Descriptive support for these amendments may be found throughout the specifications and the claims as filed. For example, support for the amendment to Claim 1, is found in paragraph [0040] and [0046] as well as original Claims 1 and 6; support for the amendment to Claim 6, is found in paragraph [0044] and [0046]; support for the amendment to Claim 7 is found in original Claim 7; support for the amendment to Claim 8 is found in original Claim 8; support for the amendments to Claims 12 and 13 is found in paragraphs [0034] and [0035] respectively; support for newly added Claims 52-54 is found at paragraphs [0040], [0044] and [0045]; support for newly added Claims 55 and 56 is found at paragraph [0042].

**INTERVIEW – FOLLOW UP**

Applicants wish to thank Examiner Meller for the courtesy of the in person Interview on February 9, 2005. As set forth in the Interview Summary, Applicants hereby (a) submit the amendments to the Claims agreed upon during the Interview, to reflect the  $\alpha$  acid content of the extracts according to the invention; and (b) provide evidence as to the  $\alpha$  acids content in beer preparations.

As requested by the Examiner, Applicants hereby provide evidence as to content of  $\alpha$  acids found in beer. Attachment A is an excerpt from M. Verzele and D. De Kekulaire, Chemistry and Analysis of Hop and Beer Bitter Acids, Developments in Food and Science (Elsevier Science Publishers B.V., 1991). At page 34, the authors state that “[t]he hop alpha

*acids as such occur in beer in concentrations up to 4 mg.L<sup>-1</sup>*<sup>1</sup> which corresponds to 0.0004%<sup>1</sup> by weight.<sup>2</sup> As agreed during the Interview, Applicants have amended the Claims to specify the range of  $\alpha$  acids content as a percentage by weight to distinguish over the art. As described in the Application as filed (see paragraph [0040]), the term “pharmaceutical grade extract” refers to “*a preparation wherein the concentration of hops extract [...] has an  $\alpha$ -acid content of about 10 to 95 percent by weight.*” Hence, beer compositions are well outside the scope of the contemplated range as discussed.

#### **REJECTIONS UNDER 35 U.S.C. § 102(E)**

Claims 1, 6-9, 12, 13, and 15 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Newmark *et al.* (U.S. Patent No. 6,391,346)<sup>3</sup> with specific reference to Col. 4, and Col. 6-7. Kindly note that Claims 1, 6-8, and Claims 12 and 13 have been amended, and Claims 9 and 15 have been canceled to reflect the understanding reached during the February 09, 2005 Interview.

Applicants kindly submit that the instant amended Claims are novel over the ‘346 Patent. As discussed, however, the rejection is moot as the ‘346 Patent was made of record and overcome earlier in the prosecution of the instant case. In the non-Final Office Action dated January 28, 2003, Claims 1, 6-9, 12, 13 and 15-17 were rejected under 35 U.S.C. §102(e) as being anticipated by the ‘346 Patent. A Declaration under 37 C.F.R. § 1.131 was provided<sup>4</sup> at that time along with supporting documentation evidencing prior invention.<sup>5</sup> A copy of that Declaration is included herewith as Attachment B.

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<sup>1</sup> It is further noted that this concentration of  $\alpha$  acids does not represent the amount of free  $\alpha$  acids, since they chemically cross-link with certain specific proteins in a complex manner. When beer is poured, the  $\alpha$  acid/protein complex supports foam formation. This phenomenon can be perceived when sipping the thick foam on a nitrogen-poured Guinness® having a distinctly more bitter taste than that found in the beer beneath.

<sup>2</sup> Briefly, the formula for weight percent (w/v) is: [Mass of solute (g) / Volume of solution (ml)] x 100. Hence, 4 mg/L correspond to 0.0004g/100mL which is equal to 0.0004%.

<sup>3</sup> Subsequent references to previously cited U.S. Patents are by citing the last three digits of the issued U.S. Patent.

<sup>4</sup> See Amendment on the record filed June 12, 2003.

<sup>5</sup> See M.P.E.P. § 706.02(b) providing that a rejection based upon 35 U.S.C. § 102(e) may be overcome by filing an affidavit or declaration.

Accordingly, Applicants respectfully request the withdrawal of these rejections under 35 U.S.C. § 102(e) based on an invention date prior to the filing date of the ‘346 Patent. Reconsideration of the Claims as amended in light of the evidence of record is respectfully requested.

**REJECTIONS UNDER 35 U.S.C. § 102(B)**

Claims 1, 6, 9, 12, 13, and 15 stand rejected under 35 U.S.C. § 102(b) as anticipated by Panzer *et al.* (U.S. Patent No. 4,554,170) with specific reference to Col. 1-2, or by Panglisch (Abstract Monatsschrift fuer Brauwissenschaft (1990) 43(1), 4-16)<sup>6</sup>.

Applicants respectfully submit that the Claims as amended are not anticipated by the art cited. Each basis of rejection is addressed individually in reference to the amended Claims in the following paragraphs for the sake of clarity.

***(a) The Amended Claims are novel over the ‘170 Patent.***

The ‘170 Patent purports to teach a method of extracting plant materials in the field of beer production (by pumping an inert gas in the pressure vessel). The ‘170 Patent seeks to solve an art recognized problem inherent to beer production. At Col. 1 lines 26-42, the ‘170 Patent states,

*“Milled hops are placed in, say, one vertically disposed pressure vessel which is then closed and connected to a supply of liquid carbon dioxide. The hops are extracted by passage of the carbon dioxide through the column. It has been found to be desirable to interrupt or stop extraction at a point at which a required percentage of the available essential oils or resin components has been extracted; at the time of said interruption or stoppage, the pressure vessel and the filter and the ancillary piping all contain a dilute solution of the extractable components of the milled hops. During decompression of the apparatus, the carbon dioxide will evaporate and this will result in the dissolved components of the extract becoming deposited on the milled hops, on the walls of the pressure vessel, on the filter and on the inner surfaces of said piping”*(underline added for emphasis).

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<sup>6</sup> Hereinafter referred to as Panglisch.

The crucial issues recognized are (a) the need to interrupt extraction at a point “*at which a required percentage of the available essential oils or resin components has been extracted*”; and the inevitable (b) deposition of the milled hops on the walls of the pressure vessel, on the filter and on the inner surfaces of the pipes. Thus, for the purposes of beer production one seeks to maximize the essential oils and resin components content. The concomitant deposition

*“is not wanted, firstly, because the dissolved components are expensive and are lost once deposited and because loss thereof is obviously undesirable and, secondly, because the deposited dissolved components take the form of a sticky, viscous substance having a soft, putty-like consistency. The deposition of said substance on the walls of the pressure vessel, the piping and the filter is bad enough and necessitates extensive cleaning being undertaken but the deposition thereof on the milled hops makes said hops difficult to deal with; not only have the partly extracted milled hops to be physically removed from the pressure vessel but also said hops must be returned to the brewer (for example, in the form of pellets).”*

(see Col. 1 lines 47-51).

In contrast, the hops extracts of the present invention are characterized among others (discussed *infra*) by the practical absence of the very resin components the ‘170 Patent seeks to maximize.

The inventors in the instant case have stumbled upon the finding that hops fractions prepared by a specific approach are associated with highly desirable biological properties. Notably, not all hops fractions would have the same biological properties. The focus of ongoing research efforts has been the elucidation of the particular process(es) and of the components (alone or in association with other chemical entities) resulting in a marked PGE<sub>2</sub> reduction for a variety of uses including *inter alia* inflammation.

The term “hops extract” is but a very general designation which appears to have obfuscated the analysis in the instant case. It is recognized that hops extracts may contain hundreds of different groups of organic compounds including the resins containing mainly hop acids, hop oils and polyphenols (see M. Verzele and D. De Kekulaire, *supra*). The CO<sub>2</sub> extraction protocol described in the ‘170 Patent involves a non-polar solvent possessing a

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polarity similar to that of hexane (see e.g., Eickoff *et al.*, Eickhoff, A and Kreuzig, R. “*The substitution of toxicologically critical solvents in the residue analysis of pesticides*” available at [www.chemsoc.org/networks/learnnet/green/docs/pesticide.pdf](http://www.chemsoc.org/networks/learnnet/green/docs/pesticide.pdf)). The resulting hops extracts contain resin components (in fact, that is what the ‘170 Patent seeks to achieve for the purposes of making palatable beer products as discussed *supra*).

A remarkable distinction lost in the liberal use of the term “hops extract” in the literature further relates to the viscosity inherent to the various hops extracts obtained by the various extraction and purification protocols. The hops extracts described in the ‘170 Patent are extremely viscous liquids. In fact, the starting materials described in the instant Application are similarly highly viscous. As such, these extracts could not be administered by the parenteral route as contemplated in the specification at paragraph [0047]. Traditionally, hops extracts have been found to be *incapable* of passing through even the largest bore needle used in human or veterinary medicine.

Beer, such as that prepared from fractions according to the ‘170 Patent is indeed derived from ‘hops extracts’ in the broadest sense of the term. It must be understood however, that the complete process of brewing virtually eliminates both the  $\alpha$  and  $\beta$  acids originally in hops and produces derivatives such as iso- $\alpha$  acids from  $\alpha$  acids and oxidation products of  $\beta$  acids (for a general overview of beer making, see for example, The Practical Brewer: A Manual for the Brewing Industry, 2nd Ed. 1980, Harold Broderich Ed., pages 136-141, and particularly page 138 discussing the conversion of  $\alpha$ -acids to iso- $\alpha$  acids and the lack of solubility associated with  $\beta$ -acids). Briefly, hops extracts containing resins and essential oils –as emphasized in the ‘170 Patent— are boiled in a kettle boil process. Beer preparation methods are designed to direct the process towards the production of iso- $\alpha$  acids and oxidation products of  $\beta$ -acids since these products (not the starting materials found in the starting hops extracts) are the components primarily responsible for the flavor and aroma desired in beer.

Notably,  $\alpha$ -acids are insoluble in water and are not present in beer in appreciable amount (during the kettle boil process they are transformed by thermal isomerization to iso- $\alpha$  acids

rendering them water-soluble) (see Inglis “*Hops and beer flavours*” IOB Technical Symposium, HoChiMinh City, Vietnam (2001), provided herewith as Attachment C (see in particular page 9 boxed text). Similarly,  $\beta$  acids are insoluble in cold water and thus, in beer. In fact, they are not found, even at trace levels, in finished beer (see Inglis, *supra* at page 4, 1<sup>st</sup> boxed text). On the contrary, oxidative products derived from  $\beta$  acids are water soluble and found in finished beer (see Inglis, *supra* at page 4, 2<sup>nd</sup> boxed text).

As shown in Example 1 of the instant Application, the hops extracts were prepared by a dimethyl sulfoxide extraction step to increase water solubility and miscibility of those very components brewers seek to convert chemically (and thus reduce dramatically --e.g., to 0.0004% in the case of  $\alpha$  acids as discussed above<sup>7</sup> -- if not eliminate as such) by the very brewing process.<sup>8</sup> The resultant hops extracts have been found to possess unique biochemical characteristics. These extracts in fact, are similar to those prepared using organic solvent based extraction protocols minus the hard resins and tannins that are not ordinarily present in the initial liquid CO<sub>2</sub>-extract of hops.<sup>9</sup> The hops fractions tested and demonstrating the ability to reduce PGE<sub>2</sub> were obtained by a remarkably different process and could not be obtained merely by the CO<sub>2</sub> extraction of hops or by the organic extraction of hops alone. The additional formulation of the extracted fractions by the addition of a pharmaceutical acceptable carrier is to prepare suitable dosage forms for the various modes of administration contemplated.

Applicants submit that the fractions of the ‘170 Patent could not, and do not, have the requisite 10-95% by weight  $\alpha$ -acid content recited in the claims as amended. Furthermore, Applicants note that the fractions of the ‘170 Patent could not exhibit the desired PGE<sub>2</sub> inhibition. In fact, the hops fractions of the ‘170 Patent without additional processing could not even be administered as contemplated in the instant invention. The addition of a “pharmaceutically acceptable carrier”, as defined in paragraph [0044] and according to the pending claims, is integral for preparations to be administered according to the invention.

<sup>7</sup> See Interview- Follow Up Section at page 8.

<sup>8</sup> See Paragraph [0055].

<sup>9</sup> See for example those described in Table 1 of the instant Application.

Accordingly, it is submitted that 'hops extracts' is merely a term of art to describe the preparations used as a starting point in the production of beer. It is further submitted that beer does not contain an appreciable  $\alpha$  or  $\beta$  acid content as naturally found in whole hops and in the hops extracts according to the instant invention.

To underscore Applicants' discovery please note that a great deal of efforts have been directed to identify those specific components within these hops extracts responsible for PGE<sub>2</sub> inhibitory effect reported in the instant Application. As shown in Attachment D (provided herewith),  $\alpha$  acids and  $\beta$  acids have been further fractionated identifying various compounds. To exemplify the point,  $\alpha$  acids have been found to convert to trans-iso- $\alpha$  acids further leading to reduced-iso- $\alpha$  acids (trans-dihydro-iso- $\alpha$ -acid) and to tetra-iso- $\alpha$  acid (trans-tetrahydro-iso- $\alpha$  acid). Testing of these fractions has identified particularly desirable  $\alpha$  and  $\beta$  acid preparations having the desired COX-2 specificity which are the subject of subsequent patent applications on the record.

***b) The Amended Claims are novel over the Panglisch Abstract.***

Panglisch is a short abstract reporting the effect of changing storage conditions of the starting hops extracts on the resultant beer aroma and flavor. Applicants respectfully submit that Panglisch is not describing hops extract compositions which are extracted to be enriched for  $\alpha$  and/or  $\beta$  acids components and/or pharmaceutically formulated according to the invention. For the reasons discussed *infra*, Applicants submit Panglisch does not anticipate the amended Claims.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 102(b) and reconsideration of the Claims in their amended form.

**REJECTIONS UNDER 35 U.S.C. § 103(A)**

Claims 1, 6-9, 12, 13, and 15-17 stand rejected under U.S.C. § 103(a) as being unpatentable over Panzer *et al.*, Panglisch, or Newmark *et al.*

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In pertinent parts the Office Action provides that it would have been obvious to use the beer in such ratios of  $\alpha$  acids to  $\beta$  acids based upon Panzer *et al.*, Panglisch, or Newmark *et al.*

Applicants respectfully aver that it would not have been obvious to use preparations of  $\alpha$  acids and/or  $\beta$  acids according to the amended claims. As discussed *infra*, none of the art cited teaches or suggests extracts having the requisite  $\alpha$  or  $\beta$  acids content. None of the art provides a suggestion or motivation to modify beer extracts to arrive at the invention described in the Application. In fact, Applicants submit that one of skill in the art would not have had a reasonable expectation of success based on the teachings of the art cited.

It is noted that the art cited does not address pharmaceutical grade extracts and pharmaceutical grade dosage forms of hops having from 10 to 95 %  $\alpha$  and/or  $\beta$  content and incorporating a pharmaceutical carrier as recited in the Claims as amended.

Accordingly, Applicants respectfully request the Examiner reconsideration of the Claims as amended in light of the evidence submitted and withdrawal of the rejections under 35 U.S.C. § 103(a).

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**CONCLUSION**

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request reconsideration of the claims and a notice to this effect. The Examiner is invited to call the undersigned to expedite prosecution.

A Request for a Three (3) Month Extension of Time, up to and including February 12, 2005 is included herewith. Pursuant to 37 C.F.R. § 1.136(a)(2), the Examiner is authorized to charge any fee under 37 C.F.R. § 1.17 applicable in this instant, as well as in future communications, to Deposit Account 50-1133. Furthermore, such authorization should be treated in any concurrent or future reply requiring a petition for an extension of time under paragraph 1.136 for its timely submission, as constructively incorporating a petition for extension of time for the appropriate length of time pursuant 37 C.F.R. § 1.136(a)(3) regardless of whether a separate petition is included.

This Response is being timely filed on February 14, 2005 since the due date, February 12, 2005, fell on a Saturday.

Respectfully submitted,



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